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EDITORIAL COMMENT

# Is it Possible to Reverse the Endothelial Dysfunction in Pulmonary Arterial Hypertension?*

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Pulmonary arterial hypertension (PAH) is a devastating disease that in its most severe form, idiopathic PAH, leads to progressive right heart failure and death within 2 to 3 years after diagnosis (1). Despite significant advances in therapeutic modalities for PAH during the past decade (2), the prognosis remains poor. In addition, although studies with animal pulmonary hypertension (PH) models and the pathology from lung tissue in PAH patients show pulmonary arteriolar occlusion, the mechanisms for these pulmonary vascular abnormalities remain unclear. Pulmonary vasoconstriction, pulmonary vascular proliferation, and remodeling of the pulmonary vessels and thrombosis in situ

See page 1566

all seem to be contributing factors to the increased pulmonary vascular resistance in PAH. The pulmonary vasoconstriction is believed to be caused by abnormal expression of pulmonary vascular smooth muscle calcium channels and endothelial dysfunction. Abnormally increased pulmonary vasoconstriction alters cell proliferation, coagulation factors, growth factors, and vasoactive mediators. An imbalance in these pulmonary vasoactive mediators promotes further pulmonary vasoconstriction and pulmonary vascular remodeling. Patients with PAH have decreased prostacyclin and nitric oxide synthase and increased thromboxane $A_2$ and endothelin-1. Furthermore, based on the mutations in the bone morphogenetic protein receptor II gene considered causal for patients with familial PAH and some patients with idiopathic pulmonary arterial hypertension (IPAH), the current dogma for the pathobiology of PAH suggests that an injury occurring in a genetically predisposed individual initiates the development of the PAH (Fig. 1). Despite the uncertainty of the exact mechanisms causing the pulmonary arteriolar obstruction, endothelial cell apoptosis could initiate microvascular degeneration or result in proliferative apoptosis-resistant endothelial cells. Thus, regeneration of the pulmonary vascular bed could be a novel therapeutic approach for reversal of the pulmonary vascular disease in patients with PAH.

One of the most interesting breakthroughs in vascular biology in recent years has been the discovery of endothelial progenitor cells (EPCs) (3). These angiogenic cells mobilize from the bone marrow in response to injury. With properties of embryonal angioblasts, EPCs are thought to have proliferative potential and may be important in vascular regeneration. The EPCs therefore may function to replace and/or restore damaged endothelial cells. In the field of cardiovascular disease, circulating EPCs are considered protective and low levels of EPCs predict poor outcome. Based on these observations, EPCs have been postulated to contribute to the maintenance of the systemic vasculature and the remodeling that accompanies new vessel growth after ischemia. It therefore would seem reasonable that if pathological processes that damage the systemic vascular endothelium result in endothelial cell detachment from mechanical injury abnormalities, EPCs as a therapeutic modality could be efficacious in restoring vascular endothelial function.

Several groups have examined whether regeneration of pulmonary microvessels in experimental PH models is possible. In the monocrotaline PH model, EPC therapy results in less pulmonary vascular disease, which could in part be caused by repair and regeneration of the pulmonary microvascular endothelium, consistent with the hypothesis that endothelial damage resulting in endothelial dysfunction and proliferation contributes to pulmonary vascular disease. Whether the decreased pulmonary vascular damage induced by EPC therapy in the monocrotaline PH model is caused by endothelial repair directly or indirectly by release of paracrine signals is unknown. Regardless, these studies support the premise that pulmonary microvascular degeneration at the precapillary level may play an important role in the development of PAH. These data also support pulmonary endothelial cells as a therapeutic target for the treatment of PAH. Exploring this hypothesis (i.e., that impairment of pulmonary vascular and endothelial homeostasis plays a significant role in the pathobiology of PAH) in the current issue of the *Journal*, Wang et al. (4) report data from a 12-week prospective randomized trial comparing the effects of intravenously infused autologous EPCs plus conventional therapy with conventional therapy alone in 31 IPAH patients. Exercise capacity assessed by the 6-min walk test was increased in the EPC-treated patients compared with the patients in the conventional therapy alone group. Hemodynamic improvement, i.e., pulmonary

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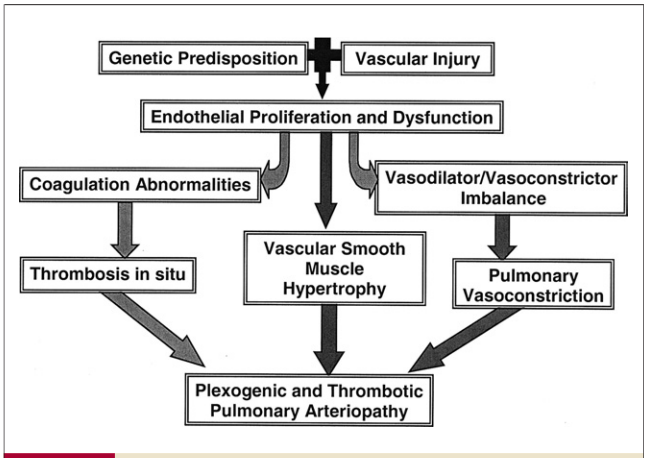


**Figure 1** **Schematic View of the Pathobiology of Pulmonary Arterial Hypertension**

arterial pressure, cardiac output, and pulmonary vascular resistance, were also improved in the EPC-treated patients versus the conventional therapy alone group. No apparent severe adverse events were reported during the 12-week study. It would be interesting to measure plasma markers assessing endothelial function, such as von Willebrand factor, soluble E-selectin, and/or soluble thrombomodulin, before and after treatment with infused autologous EPCs in PAH patients to investigate whether markers of endothelial function improve, and if so, whether the improvement in endothelial function correlates with the clinical and/or hemodynamic improvement.

As we investigate novel therapeutic strategies for improving PAH treatment, EPCs offer an intriguing approach. In addition, the revolution in molecular medicine has generated enthusiasm for gene therapy as a novel form of drug delivery that enlists the synthetic machinery of the patient's cells to produce a therapeutic agent. Zhao et al. (5) reported that treatment with endothelial nitric oxide synthase (eNOS)-transduced EPCs was more effective than treatment with EPCs alone in reversing pulmonary vascular disease in the rat monocrotaline PH model. The increased efficacy with the eNOS gene transfer provides further support for the role of endothelium-derived nitric oxide in pulmonary vascular regeneration. Zhao et al. (5) suggest that the loss of pulmonary arteriolar continuity at the precapillary level may be an early event directly contributing to the increase in pulmonary vascular resistance because of the loss of vessels in the pulmonary microcirculation. Based on these animal studies, and the pilot study by Wang et al. (4) in IPAH patients, further investigation is needed to explore regenerative cell-based strategies for the treatment of patients with severe progressive PAH in whom the prognosis remains poor despite currently available therapies.

It is an exciting time in the history of clinical development for PAH therapies. Before 1996, treatment for IPAH was limited to conventional therapy (i.e., digoxin, diuretics, anticoagulation, supplemental oxygen when clinically indicated, calcium channel blockers in select patients, and lung or heart-lung transplantation). Intravenous epoprostenol was then added to the treatment algorithm for PAH as a palliative bridge to transplantation. Over the past decade, prostacyclin analogues, selective and nonselective endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors have been developed. These drugs increase exercise capacity, improve functional capacity and quality of life, improve hemodynamic parameters, and increase survival in PAH. However, exercise capacity remains significantly impaired in at least 50% of patients, similar numbers of patients remain at least at functional class III, patients continue to have frequent hospitalizations for worsening PAH, and pulmonary hemodynamics remain significantly abnormal. Despite improved survival, survival remains unacceptable. We need to look to the future and to study combination therapy, early therapy, and other novel pathophysiologic targets (e.g., platelet-derived growth factor inhibitors, rho-kinase inhibitors, vasoactive intestinal peptide, 5HT2$\beta$-antagonists) and other immunotherapeutic agents, as we strive to achieve near-normal exercise capacity, functional class I, marked reductions in hospitalizations and pulmonary artery pressures, and a quality of life and survival close to normal.

If EPC therapy can restore endothelial function, this approach could conceivably restore imbalances in vasoactive mediators. Current therapeutic approaches have focused on one pathway at a time, (i.e., the prostacyclin pathway, the nitric oxide pathway, or the endothelin pathway). Therapeutic approaches integrating these 3 pathways are the basis for combination therapy. Furthermore, because the pathobiology of PAH is considered multifactorial with genetic risk factors, environmental risk factors, and associated conditions, it is not unreasonable to suspect that a given therapeutic approach will not be efficacious for all patients. Studies evaluating various disease-specific targeted PH therapies are needed to individualize treatment. Therefore, it would not be unreasonable that specific gene therapies may be found to be more efficacious in specific patients (e.g., eNOS gene therapy combined with EPCs as a therapeutic approach in patients with decreased expression of nitric oxide synthase).

With these recent advances in the understanding of the mechanisms of disease development in PAH as well as in its treatment, one day, hopefully in the not-too-distant future, we may be able to prevent and cure this once uniformly fatal disease. However, one must remain cognizant of risk-benefit considerations for all treatment options being considered for individual patients.

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JACC Vol. 49, No. 14, 2007
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